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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	OC01017Q
First Inventor or Application Identifier	Mohamed H. Ragab
Title	Improved Cancer Treatment With Temozolomide
Express Mail Label No.	EL226881838US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. [X] * Fee Transmittal Form *(e.g., PTO/SB/17)* *(Submit an original and a duplicate for fee processing)*
2. [X] Specification [Total Pages 8] *(preferred arrangement set forth below)*
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) *(35 U.S.C. 113)* [Total Sheets]
4. Oath or Declaration [Total Pages 3]
   a. [X] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d)) *(for continuation/divisional with Box 16 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

5. [ ] Microfiche Computer Program *(Appendix)*
6. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Copy
   b. [ ] Paper Copy (identical to computer copy)
   c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. [ ] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
9. [ ] English Translation Document *(if applicable)*
10. [X] Information Disclosure Statement (IDS)/PTO-1449 [X] Copies of IDS Citations
11. [X] Preliminary Amendment
12. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
13. [ ] * Small Entity Statement(s) *(PTO/SB/09-12)* [ ] Statement filed in prior application, Status still proper and desired
14. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
15. [X] Other: Cover Sheet (1 page)

16. **If a CONTINUING APPLICATION,** *check appropriate box, and supply the requisite information below and in a preliminary amendment:*

[ ] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No: ____/____

Prior application information: Examiner _____ *Group / Art Unit:* _____

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

17. CORRESPONDENCE ADDRESS

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Signature	Arthur Mann	Date	March 27, 2000

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PATENT CASE: **OC01017Q**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: ***MOHAMED H. RAGAB***	Group Art Unit: (To Be Assigned)
For Patent: **IMPROVED CANCER TREATMENT WITH TEMOZOLOMIDE**	Examiner: (To Be Assigned)
Serial No.: (To Be Assigned)	
Filed: March 27, 2000	Date: March 27, 2000

Schering-Plough Corporation
Kenilworth, New Jersey 07033

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Please enter the following amendment prior to examining the above-identified application:

In the Specification

On page 1, before "BACKGROUND OF THE INVENTION," insert the following:

--This application claims the benefit of U.S. Provisional Application No. 60/126,808, filed March 30, 1999.--

Remarks

The amendment has been made to refer to Applicant's earlier provisional application.

Respectfully submitted,

Arthur Mann
Reg. No. 35,598
Attorney for Applicant
(908) 298-2903

EXPRESS MAIL NO. EL226881838US

5741_1

Attorney Docket Number OC01017Q

PATENT APPLICATION

IMPROVED CANCER TREATMENT WITH TEMOZOLOMIDE

INVENTORS:

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ASSIGNEE: Schering Corporation

"Express Mail" Label No. EL226881838US

Date of Deposit: March 27, 2000

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IMPROVED CANCER TREATMENT WITH TEMOZOLOMIDE

This invention relates to the treatment of cancer and in particular to the treatment of cancers with Temozolomide.

BACKGROUND OF THE INVENTION

Temozolomide is known for its anti-tumor effects. For example, in one study clinical responses were achieved in 17% of patients having advanced melanoma (Newlands et al. Br. J. Cancer 65 (2) 287-291 (1992)). In another study, a clinical response was achieved in 21% of patients with advanced melanoma (Journal of Clinical Oncology, Vol 13, No. 4 (April), 1995, pp 910-913). Treatment of gliomas in adults with temozolomide is also known (Eur. J. Cancer 1993; 29A:940). Treatment of the following cancers in adults with temozolomide has also been disclosed: metastatic melanoma; high grade glioma, glioblastoma and other brain cancers; lung cancer; breast cancer; testIcular cancer; colon and rectal cancers; carcinomas; sarcomas; lymphomas; leukemias; and mycosis fungoides. Prior to the present invention, the generally accepted method for administering temozolomide was to administer it over a 28 day cycle, in which it is administered daily for the first 5 days of the cycle, followed by 23 days of rest, in which it is not administered. Newlands et al., Br. J. Cancer 65 (2) 287-291 (1992). A clinical trial has also been carried out wherein temozolomide was administered continuously as a daily dose for 6-7 weeks in conjunction with radiation treatment. See, e.g., Brock et al., Cancer Research 58, 4363-4367 (1998).

SUMMARY OF THE INVENTION

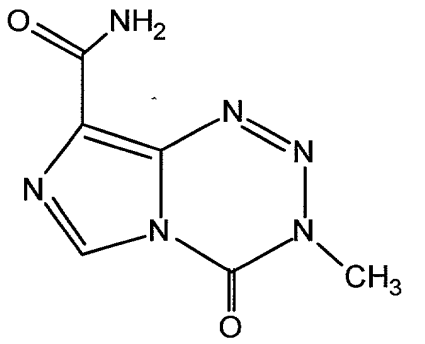
The present invention provides a method for treating a patient afflicted with cancer, comprising administering temozolomide to said patient for at least two cycles of a cyclical dosing schedule, wherein each cycle comprises a dosing period of 5 to 25 days, in which temozolomide is administered daily, at a dose of 40 to 150 mg/m^2/day, followed by a rest period of 5 to 14 days in which temozolomide is not administered.

In a further aspect of the present invention, a medical kit for administering temozolomide is provided, comprising printed instructions for administering temozolomide according to the cyclical dosing schedule set forth above, and a supply of temozolomide in

dosage units for at least one cycle, wherein each dosage unit comprises 5 to 250 mg of temozolomide and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

The term "temozolomide" is intended to mean a compound having the formula:



One chemical name for temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo-[5,1-d]1,2,3,4-tetrazin-8-carboximide. The synthesis of temozolomide is well known. See, for example, Stevens et al., J. Med. Chem, 1984, 27, 196-201 and Wang et al., J. Chem. Soc., Chem. Commun., 1994, pp 1687-1688.

As used herein, the term "$mg/m^2/day$" refers to a daily dose measured in milligrams per square meter of body surface area of the patient.

As used herein, the term "patient" refers to a mammal, preferably a human.

Examples of cancers treatable by this invention include, but are not limited to melanoma; high grade glioma, glioblastoma and other brain cancers; lung cancer; breast cancer; testicular cancer; gastro intestinal cancers including colon, rectal, pancreatic, and gastric cancers, hepatocellular carcinoma; head and neck cancers; prostate cancer, renal cell carcinoma; adenocarcinoma; sarcomas; lymphomas; leukemias; and mycosis fungoides. This invention contemplates treating these cancers and other cancers at any stage from the discovery of the cancer to the advanced stage. The invention includes treatment of the primary cancer and metastases thereof.

A person afflicted with cancer may exhibit one or more of the following signs or symptoms:

(a) presence of cancerous tumor,

(b) fatigue,

(c) pain,

(d) decreased performance status from tumor burden, and

(e) the well known symptoms associated with each specific cancer.

The rest period according to the present invention (the portion of the cycle in which temozolomide is not administered) is 5 to 14 days, more preferably, 5 to 10 days, most preferably, 1 week. The dosing period according to the present invention is 5 to 25 days, more preferably, 1, 2, or 3 weeks, most preferably 1 or 3 weeks. The treatment cycles may be continued for as long as needed to cause the cure, remission, or elimination of the cancer that is being treated.

The daily dose during the dosing period of the present invention is 40 to 150 mg/m^2/day, more preferably 40 to 125 mg/m^2/day, most preferably 75 to 125 mg/m^2/day. The daily dose may be administered as a single dose, or as multiple doses adding up to the single dose. For example, a daily dose of 100 mg/m^2 may be administered as two doses of 50 mg/m^2, or four doses of 25 mg/m^2. The selected dosage may be decreased, if intolerable side effects or hematologic toxicity are encountered.

A common, but tolerable side effect of temozolomide is nausea and vomiting. This can be alleviated by administering an anti-emetic in conjunction with the temozolomide. It is preferred that the anti-emetic Ondansetron be given p.o. in a dose of about 8 mg about 30 minutes before temozolomide administration. Other anti-emetics such as Hasaldol, Benadryl, and Ativan may also be used as needed.

Temozolomide is preferably administered orally in capsule form wherein it is admixed with conventional pharmaceutical carriers. Preferred temozolomide capsule formulations are:

Ingredient	mg/Capsule			
temozolomide	5	20	100	250
Anhydrous Lactose NF	132.8	182.2	175.7	154.3
Sodium Starch Glycolate NF	7.5	11.0	15.0	22.5
Colloidal Silicon Diozide NF	0.2	0.2	0.3	0.7
Tartaric Acid NF	1.5	2.2	3.0	9.0
Steric Acid NF	3.0	4.4	6.0	13.5
Capsule Size*	3	2	1	0

* White opaque, preservative-free, two-piece hard gelatin capsules

Other forms of administration of temozolomide, as they become available, are contemplated, such as by IV injection or infusion, intrathecally, by sustained release dosage form, syrup, suppository, transdermal, nasal spray, etc.. Any form of administration will work so long as the proper dosage is delivered without destroying the temozolomide.

It may be preferable in some instances to administer an initial large oral bolus dose of about 100 to 500 mg/m^2 prior to beginning the cyclical dosing regimen of the present invention.

The medical kit in accordance with the present invention may be in any form suitable for providing a supply of temozolomide for at least one cycle, together with written instructions for administering it according to the cyclical dosing schedule. Examples include, but are not limited to, various containers (e.g., bottles, cartons, blister packs, and ampules) either accompanied by a package insert describing the cyclical dosing instructions, or wherein the cyclical dosing instructions are printed on, or affixed to the container.

The following examples illustrate the foregoing invention, although such examples should not be construed as limiting the scope of the invention.

EXAMPLE 1

To a patient suffering from glioma, administer temozolomide for a period of twelve 14-day cycles, each cycle consisting of a one week period in which temozolomide is administered at the rate of 100 mg/m^2/day, followed by a one week rest period in which temozolomide is not administered.

EXAMPLE 2

To a patient suffering from glioma, administer temozolomide for a period of six 28-day cycles, each cycle consisting of a three week period in which temozolomide is administered at the rate of 100 mg/m^2/day, followed by a one week rest period in which temozolomide is not administered.

EXAMPLE 3

To a patient suffering from advanced melanoma, administer temozolomide for a period of twelve 14-day cycles, each cycle consisting of a one week period in which temozolomide is administered at the rate of 100 mg/m^2/day, followed by a one week rest period in which temozolomide is not administered.

EXAMPLE 4

To a patient suffering from advanced melanoma, administer temozolomide for a period of six 28-day cycles, each cycle consisting of a three week period in which temozolomide is administered at the rate of 100 mg/m^2/day, followed by a one week rest period in which temozolomide is not administered.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WE CLAIM:

1. A method for treating a patient afflicted with cancer, comprising administering temozolomide to said patient for at least two cycles of a cyclical dosing schedule, wherein each cycle comprises a dosing period of 5 to 25 days, in which temozolomide is administered daily, at a dose of 40 to 150 mg/m^2/day, followed by a rest period of 5 to 14 days in which temozolomide is not administered.

2. The method of claim 1, wherein the rest period is 5 to 10 days.

3. The method of claim 2, wherein the daily dose is 75 to 125 mg/m^2/day.

4. The method of claim 1, wherein the rest period is one week.

5. The method of claim 4, wherein the daily dose is 75 to 125 mg/m^2/day.

6. The method of claim 1, wherein the dosing period is one, two, or three weeks.

7. The method of claim 6, wherein the rest period is one week.

8. The method of claim 7, wherein the dosing period is one week.

9. The method of claim 8, wherein the daily dose is 75 to 125 mg/m^2/day.

10. The method of claim 7, wherein the dosing period is three weeks.

11. The method of claim 10, wherein the daily dose is 75 to 125 mg/m^2/day.

12. A medical kit for administering temozolomide, comprising:

(a) printed instructions for administering temozolomide to a patient afflicted with cancer for at least two cycles of a cyclical dosing schedule, wherein each cycle comprises a dosing period of 5 to 25 days, in which temozolomide is administered daily, at a dose of 40 to 150 mg/m^2/day, followed by a rest period of 5 to 14 days in which temozolomide is not administered; and

(b) a supply of temozolomide in dosage units for at least one cycle, wherein each dosage unit comprises 5 to 250 mg of temozolomide and a pharmaceutically acceptable carrier.

13. The medical kit of claim 12, wherein the instructed rest period is 5 to 10 days.

14. The medical kit of claim 13, wherein the instructed daily dose is 75 to 125 mg/m^2/day.

15. The medical kit of claim 12, wherein the instructed rest period is one week.

16. The medical kit of claim 15, wherein the instructed daily dose is 75 to 125 mg/m^2/day.

17. The medical kit of claim 15, wherein the instructed dosing period is one, two, or three weeks.

18. The medical kit of claim 15, wherein the instructed dosing period is one week, and the instructed daily dose is 75 to 125 mg/m^2/day.

19. The medical kit of claim 15, wherein the instructed dosing period is three weeks, and the instructed daily dose is 75 to 125 mg/m^2/day.

ABSTRACT

A method for treating a patient afflicted with cancer is provided, in which temozolomide is administered to the patient for at least two cycles of a cyclical dosing schedule, wherein each cycle has a dosing period of 5 to 25 days, in which temozolomide is administered daily, at a dose of 40 to 150 mg/m^2/day, followed by a rest period of 5 to 14 days in which temozolomide is not administered.

Also provided is a medical kit for administering temozolomide, having printed instructions for administering temozolomide according to the cyclical dosing schedule set forth above, and a supply of temozolomide in dosage units for at least one cycle, wherein each dosage unit contains 5 to 250 mg of temozolomide and a pharmaceutically acceptable carrier.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☒ Declaration Submitted with Initial Filing **OR** ☐ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16 (e)) required)

Attorney Docket Number	OC01017Q
First Named Inventor	Mohamed H. Ragab
COMPLETE IF KNOWN	
Application Number	/
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED CANCER TREATMENT WITH TEMOZOLOMIDE

(Title of the Invention)

the specification of which
☒ is attached hereto
OR
☐ was filed on (MM/DD/YYYY) _____ as United States Application Number or PCT International Application Number _____ and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto:

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	
60/126,808	03/30/99	☐ Additional provisional application numbers are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

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Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle [if any])	Family Name or Surname
Mohamed H.	Ragab

Inventor's Signature	Mohamed H. Ragab					**Date**	3/17/00
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Post Office Address							
City	Westfield	**State**	NJ	**ZIP**	07090	**Country**	U.S.A.

☐ Additional inventors are being named on the ____supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

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DECLARATION

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